REMARKS

Claims 1 and 5-17 are pending[1]. Claims 12-14, due to a Restriction Requirement, have been withdrawn from consideration. Claims 1, 5-11 and 15-17 are rejected under 35 U.S.C. § 103. Applicants address each basis for rejection as follows.

Amendments to the claims

Claim 1 has been amended to require that the hydroxyapatite "substantially retains the daughter nuclide after decay of the parent nuclide." Support for this amendment is found, for example, at page 4, lines 19-20 of the specification as filed. No new matter has been added by the present amendment.

Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Rejections under 35 U.S.C. § 103

The Claims 1, 5-11, and 15-17 are rejected under 35 U.S.C. § 103 as unpatentable over the combination of (1) U.S. Patent No. 5,609,850 ("Deutsch") with McDevitt (Eur. J. Nuclear Med. 25:1341-1351, 1998; "McDevitt") or (2) U.S. Patent No. 5,300,281 ("McMillan"), with U.S. Patent No. 4,970,062 ("Atcher") and U.S. Patent Application Publication No. US 2004-0258614 ("Line"). Applicants address each basis for the obviousness rejection, in turn, below.

Deutsch and McDevitt

The Office asserts that claims 1, 5-11, and 15-17 are obvious over the combination of Deutsch with McDevitt and states (pages 4 and 5):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate [an] alpha-emitting radionuclide such as

[1] The Office indicates that claims 1-11 and 15-17 are under examination, but claims 2-4 were cancelled in Applicants' February 18, 2011 amendment.

> ^{211}At, ^{212}Bi, ^{223}Ra, ^{225}Ac and ^{212}Pb into [the] Deutsh [*sic*; Deutsch] composition. The person of ordinary skill in the art would have been motivated to make those modifications because Michael [McDevitt] teaches that alpha-emitters have considerably shorter half-lives than the commonly used beta-emitters and relevant pharmacokinetic information will be obtained if imaging and/or sampling starts immediately after administration (page 1346) and the cytotoxicity induced by alpha-emitters is far more selective. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success.

Applicants respectfully disagree and submit that the claims as amended are free of this basis for the obviousness rejection.

Deutsch relates to compositions comprising apatite particles for use in medical diagnostic imaging. Incorporation of a range of possible metal ions into the apatite structure is disclosed in column 2, lines 5 to 8, although it is clear from the list further down the page, in lines 44 to 50, that the radionuclides listed in claim 1 of the current application do not fall within those envisaged by Deutsch. Applicants submit, as explained below, that neither Deutsch nor McDevitt addresses maintaining control over alpha-emitting radionuclides and their decomposition products.

Claim 1, as amended, requires the hydroxyapatite (HA) to substantially retain the daughter nuclide after decay of the parent nuclide. The fate of daughter isotopes, which are themselves often radioactive, is of key importance for the safety and tolerability of a radiopharmaceutical, as discussed in the application as filed (see e.g., page 3, lines 1 to 30). Neither Deutsch nor McDevitt indicates that using hydroxyapatite to incorporate alpha-emitting radionuclides would be capable of addressing this issue and hence, as further explained below, the solution encompassed by the presently pending claims cannot be considered obvious in view of these documents.

The problem of retaining daughter nuclei after alpha-decay (all of the nuclei listed in claim 1 either decay by alpha-emission, or directly generate short lived nuclei which do) is of great clinical significance. The common general knowledge at the filing date of

the current application was that the nuclear recoil, produced when a massive alpha-particle is emitted at around 2% of the speed of light, is sufficient to break chemical bonds and therefore finding suitable systems which could withstand this in order to retain the daughter nuclide represented a great challenge. The energy imparted to the daughter nucleus after alpha-decay is typically around 100 KeV whereas covalent bond energy is closer to 4 – 10 KeV.

Surprisingly, the present inventors found that alpha-emitters within HA particles, which are held by a multitude of non-covalent interactions rather than a single strong bond, are retained to a much greater extent following decay than had been shown for other alpha-emitter delivery systems. This is discussed in the specification starting at page 4, line 13 and is demonstrated in Example 2. In Example 2, ^{223}Ra was stably retained to 93.2% in HA particles after 2 weeks (the half-life of ^{223}Ra is about 11.5 days, so around 57% of the nuclei would have decayed in this time), indicating a very high retention, which is of great importance because the decay of ^{223}Ra leads to 3 further alpha-emissions before stable ^{207}Pb is reached.

It is important to appreciate that the radionuclides in the HA of the current invention are not covalently bonded to the apatite, but are stably trapped within it (see page 4, lines 28-36, of the application as filed). Applicants submit that not only is this solution nonobvious to the skilled worker in view of Deutsch and McDevitt, but, also, even if the skilled worker was to combine the teachings of these two documents, the worker would not arrive at an identical solution.

In Deutsch, the metal ions are incorporated into the apatite in one of two ways: by replacement of the calcium, or by adsorption onto the particle surface. Nowhere in this document is it suggested that the metal ion might be trapped within the HA particle.

Moreover, some of the radionuclides listed in pending claim 1 are substantially larger in size than those envisaged for use in Deutsch. Given that the inclusion of the metal ions within the apatite was not even considered by Deutsch, the skilled worker

would have no guidance as to whether or not it was even feasible to do so. The skilled worker would not know that there was enough space within the HA to accommodate the particles encompassed by the present claims.

For the above reasons, Applicants submit that Deutsch and McDevitt, alone or in combination, fail to teach or suggest that HA might be able to stably retain the daughter nuclei of alpha radionuclides following emission. Further, even if the teachings of Deutsch and McDevitt *were* combined the skilled worker would be motivated to generate hydroxyapatite in which the radionuclide either took the place of the calcium atoms or had the radionuclide adsorbed onto the surface. Such complexes, however, as explained above, would not substantially retain the daughter nuclide after decay of the parent nuclide, as required by the claims as amended. Accordingly, the combination of Deutsch with McDevitt does not teach or suggest every element of the claimed invention and cannot render the claims, as amended, obvious. This basis for the rejection under 35 U.S.C. § 103 should be withdrawn.

McMillan, Line, and Atcher

The Office asserts that claims 1, 5-11, and 15-17 are obvious over the combination of McMillan, Line, and Atcher. In particular, the Office asserts (page 7; citations omitted):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the alpha-emitting radionuclides into McMillan's radioactive composition. The person of ordinary skill in the art would have been motivated to make those modifications because Line teaches that coupling of alpha emitter radionuclides to microsphere particles allow[s] the delivery of high intensity tumoricidal doses of radiation without exposure of normal liver tissue. As evidenced by Atcher et al. clinically alpha emitting radionuclides have the potential to be more efficacious than other beta-emitting radionuclides.

Applicants respectfully submit that the claims as amended are free of this basis for

rejection.

McMillan discloses radioactive compositions containing a calcified matrix, such as hydroxyapaptite, for use in the treatment of rheumatoid arthritis. The HA acts as a carrier for the radionuclides, however, the teaching of this document is restricted to beta-emitters which do not fall within the scope of the pending claims. The Office asserts, however, that because Line teaches that it is possible to couple alpha-emitting radionuclides to microsphere particles to deliver high-intensity radiation, the skilled worker would consider, with a reasonable expectation of success, replacing the beta-emitters in McMillan with an alpha-emitter. Atcher is cited as evidence that it was known in the art that alpha-emitters have the potential to be more efficacious than beta-emitters due to their far lower penetration range within the body, leading to reduced travel to surrounding healthy tissue. The Office asserts Examiner that it would have been obvious to the skilled worker to replace the beta-emitters in the compositions of McMillan with alpha-emitters so as to provide an improved radiotherapeutic. Applicants respectfully disagree with this line of reasoning.

All of the cited documents fail to address the key difference between beta-emitters and alpha-emitters in the context of the objective technical problem: that being control of daughter isotopes which are often themselves radioactive, which is critical when administering an isotope to the body and that the issue of nuclear recoil is not relevant to beta-emitters. It is essential to appreciate, in assessing the presently claimed invention, that the nuclear recoil provided by emission of an electron, having a vanishingly small mass, is insignificant in comparison with that imparted by an emitted helium nucleus. Studies of beta-emitters thus provide no guidance as to the capabilities of similar complexes to retain radionuclei after alpha-decay. Simply because McMillan teaches that HA acts as a useful carrier for beta-emitting radionuclides, does not render it suitable for use with alpha-emitters without some specific teaching or suggestion to this effect. In particular, McMillan does not teach the stable retention of daughter nuclei. The other

cited documents fail to provide this necessary teaching. As such, the combination of the cited art fails to provide any guidance as to how HA can be used to substantially retain the daughter nuclide after decay of the parent nuclide, as required by the amended claims.

Further, as noted above in response to the rejection based on Deutsch and McDevitt, if the skilled worker was to combine the cited art, the worker would not arrive at the solution to the objective technical problem as presented in the current application. Although the Office correctly points out that Line discloses microspheres which comprise alpha-emitting radionuclides, the radionuclides are not trapped within the microparticles but are *covalently bonded* to the core of the particle via a biocompatible polymer.

Applicants submit that, if the skilled worker was considering the teaching of Line together with McMillan and the common general knowledge at the filing date of the application, he would not inclined to try to use HA as a carrier for a covalently-bonded alpha-emitter because, as noted above, nuclear recoil upon alpha emission was known to provide many times the energy required to break chemical bonds. The present inventors solved the problem of daughter radionuclide retention by trapping the alpha-emitter within the HA, with only non-covalent interactions to hold it in place. Nothing in the cited art, even if combined, would lead a skilled worker to generate anything but a radionuclide covalently-bonded to HA. There would not have been any motivation for the skilled worker to make such a complex as it would not be expected to substantially retain the daughter nuclide after decay of the parent nuclide. Substantial retention of the daughter is required by the claims as amended.

Applicants submit that the presently claimed invention is nonobvious over the combination of McMillan, Atcher, and Line. This basis for the obviousness rejection may also be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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